

**Amendments to the Claims**

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

1(Previously presented). A conjugate of (1) at least one therapeutic agent for joint diseases and (2) hyaluronic acid, a hyaluronic acid derivative or a salt thereof, wherein said at least one therapeutic agent for joint diseases covalently binds to a carboxyl group of hyaluronic acid, the hyaluronic acid derivative or the salt thereof via a spacer.

Claim 2 (Cancelled).

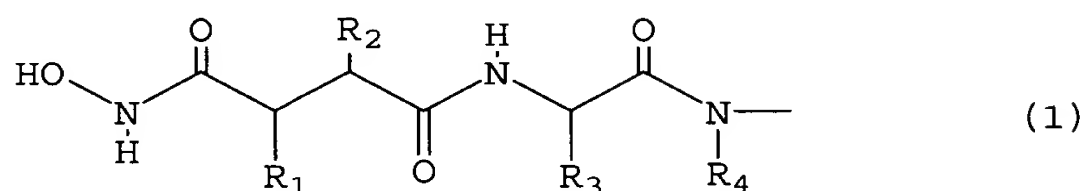
3(Previously presented). The conjugate of claim 1, wherein the therapeutic agent for joint diseases is a matrix metalloprotease inhibitor.

Claim 4 (Cancelled).

5(Previously presented). The conjugate of claim 3, wherein the weight ratio of the matrix metalloprotease inhibitor to the entire conjugate is 0.01 to 50%.

6(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue.

7(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue represented by the general formula (1):



wherein

R<sub>1</sub> is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R<sub>2</sub> is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R<sub>3</sub> is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group; and

R<sub>4</sub> is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

8(Previously presented). The conjugate of claim 1, wherein the spacer is represented by the general formula (2):



wherein

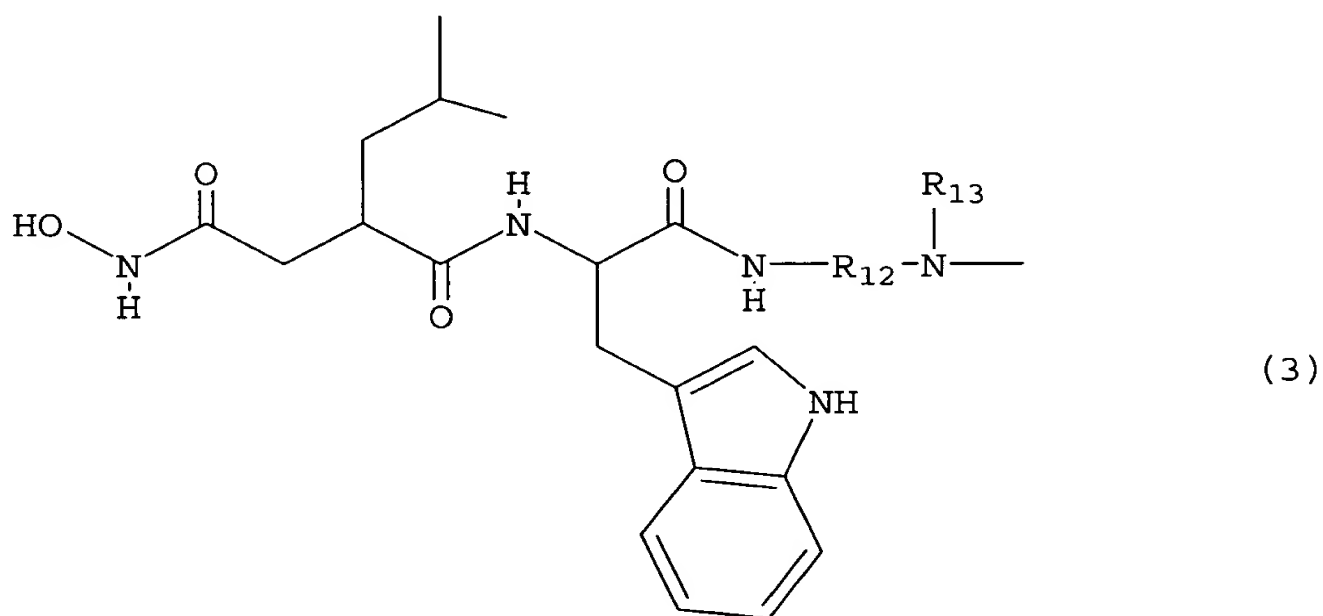
R<sub>5</sub> is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

$R_6$  is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

$R_7$  is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

$R_8$  is an oxygen atom, a sulfur atom or  $NR_9$ , wherein  $R_9$  is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

9(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor and the spacer constitute a moiety represented by the general formula (3):



wherein

$R_{12}$  is a straight-chain or branched-chain alkylene group having 2 to 23 carbon atoms into which one imino group and/or one to four oxygen atoms may be inserted; and

R<sub>13</sub> is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

10(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor in the form of a conjugate with hyaluronic acid, a hyaluronic acid derivative or a salt thereof inhibits a matrix metalloprotease *in situ*.

11(Previously presented). A method for preparing the conjugate of claim 1 comprising binding a site of the therapeutic agent for joint diseases that does not affect the activity of the agent to a carboxyl group, a hydroxyl group or a functional group at the reducing end of hyaluronic acid, a hyaluronic acid derivative or a salt thereof by direct chemical reaction or via a spacer.

12(Currently amended). A pharmaceutical composition comprising the conjugate of any one of claims 1, 3, 5-10, [[18-21]] 18, 19, 23 and 24 and a pharmaceutically acceptable diluent.

Claims 13-16 (Cancelled).

17(Currently amended). A method for treating a patient having a joint disease comprising administering a pharmaceutical composition containing a pharmaceutically effective amount of the

conjugate of any one of claims 1, 3, 5-10, ~~[[18-21]]~~ 18, 19, 23 and 24 as the effective ingredient to the patient.

18(Previously presented). The conjugate of claim 1, wherein the therapeutic agent for joint diseases is selected from the group consisting of a cyclooxygenase 2 inhibitor, an antirheumatic agent and a matrix metalloprotease inhibitor.

19(Currently amended). The conjugate of claim 1, wherein the ~~spacer bond~~ between ~~at least one therapeutic agent for joint diseases~~ said spacer and said hyaluronic acid, ~~a hyaluronie acid~~ or derivative or ~~[[a]]~~ salt thereof is selected from the group consisting of an amide bond, an ether bond and a sulfide bond.

Claims 20 and 21 (Cancelled).

22(Previously presented). A method of treating a joint disease in a patient in need thereof, comprising administering a pharmaceutical composition to said patient in an amount sufficient for said treatment, wherein said pharmaceutical composition comprises a conjugate in accordance with claim 1.

23(Previously presented). The conjugate of claim 1, wherein component (1) is a single therapeutic agent for joint disease.

24(Previously presented). The conjugate of claim 1, wherein component (2) is hyaluronic acid or a salt thereof.

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Reply to Office Action of July 1, 2004

25(Previously presented). The method of claim 17,  
wherein the joint disease is selected from the group consisting  
of osteoarthritis, rheumatoid arthritis, and scapulohumeral  
periarthrititis.